(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number
WO 03/028718 A1

(51) International Patent Classification[7]: A61K 31/40, 31/715, C07D 401/12

(21) International Application Number: PCT/US02/31297

(22) International Filing Date: 1 October 2002 (01.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/326,368 1 October 2001 (01.10.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/028718 A1

(54) Title: NOVEL FORMULATIONS OF CARVEDILOL

(57) Abstract: This invention relates to a novel formulations comprising carvedilol and methods of using these formulations to treat hypertension, congestive heart failure and angina.

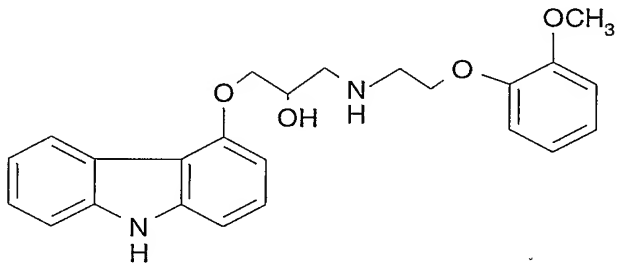
NOVEL FORMULATIONS OF CARVEDILOL

Field of the Invention

This invention relates to novel formulations of carvedilol and to the use of such formulations in the treatment of hypertension, congestive heart failure and angina.

Background of the Invention

The compound, 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, is known by the name " carvedilol" and is the subject of U.S. Patent No. 4,503,067 (the '067 patent), issued March 5, 1985. This compound has the following structure:



Carvedilol is useful in the treatment of hypertension, congestive heart failure and angina.

The current commercial formulation for carvedilol is immediate release, and it is administered twice daily. The immediate release formulation of carvedilol is rapidly and extensively absorbed following oral administration, with the terminal elimination half-life ranging between 7-10 hours. A once-daily dosing formulation for carvedilol is commercially desirable, would simplify a patient's dosing regimen and may improve compliance rates. Thus, it is an object of the instant invention to develop a once-daily dosing formulation for carvedilol.

According to the instant invention, it has been found that carvedilol can be formulated in novel formulations for once-daily dosing.

Summary of the Invention

The present invention provides for the use of cyclodextrin complexes in formulations comprising carvedilol.

This invention also provides for the use of such formulations for the treatment of hypertension, congestive heart failure and angina.

Brief Description of the Figures

The mean plasma concentrations versus time profiles of carvedilol following bolus oral and intracolonic administration of the instant formulations at 5mg/Kg in dogs are presented in Figure 1. Figures 2 shows the plasma concentration of carvedilol following administration of an oral suspension at 5mg/Kg. Figures 3 shows the plasma concentration of carvedilol following intracolonic administration of the captisol complex at 5mg/Kg. Figures 4 shows the plasma concentration of carvedilol following intracolonic administration of the encapsin complex at 5mg/Kg.

Description of the Invention

According to the present invention, compositions of carvedilol are provided comprising carvedilol-cyclodextrin complexes. The composition may then be formulated, for example, in the form of tablets or capsules. Orally administrable formulations are preferred.

Importantly, the present invention provides for a formulation comprising carvedilol-cyclodextrin complexes.

As used herein, the term "carvedilol-cyclodextrin complexes" refers to Carvedilol-Captisol®, sulfobutylether beta-cyclodextrin, or Carvedilol-Encapsin, hydroxypropyl beta-cyclodextrin complexes.

The compositions containing the carvedilol-cyclodextrin complexes, thus produced, are then used in tablets for oral administration in a unit dose. These oral tablets comprise conventional controlled release formulations, such as tablets, having a sustained release or an enteric coating, or otherwise modified to control the release of the active compound, for example by the inclusion of gel forming polymers or matrix forming waxes.

Tablets for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers and diluents (tableting or compression aids), lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to techniques well known in the art.

These oral formulations may be prepared by conventional methods of blending, filling, tableting, or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, well known in the art.

Thus, the present invention provides for the use of a pharmaceutically acceptable organic acid in the formulations comprising carvedilol. The formulation is adapted for oral administration. The formulation is presented as a unit dose. Such a formulation is taken once or twice daily, preferably once daily. The preferred unit dosage forms include tablets comprising beween about 25-50 mg of carvedilol.

No unacceptable toxicological effects are expected when carvedilol is administered in accordance with the present invention.

The following examples are illustrative of the instant invention. These examples are not intended to limit the scope of this invention as defined hereinabove and as claimed hereinbelow.

EXAMPLES

Summary

The objective of this study was to determine whether the increased solubility of Carvedilol-Captisol®, sulfobutylether beta-cyclodextrin, or Carvedilol-Encapsin, hydroxypropyl beta-cyclodextrin,complexes in pH 6.0 phosphate buffer results in the enhanced absorption of carvedilol in the lower GI tract. There is a ten fold increase in the solubility of carvedilol when complexed with Captisol®, compared to Encapsin. These studies were conducted with beagle dogs surgically implanted with colonic ports for dosing. An oral dosing of a suspension of Carvedilol in 1% methocel was also performed in order to determine the ratio of intracolonic versus oral absorption.

Background

Carvedilol is a novel, multiple-action cardiovascular agent that is being developed jointly by SmthKline Beecham and Boehringer Mannheim GmbH. Carvedilol is rapidly absorbed following oral administration in the rat and dog. Due to substantial first pass metabolism, the absolute bioavailability of Carvedilol in the rat and dog is low (20-25% and 10-30%, respectively).

The GI regional absorption study conducted in man with a gelatin suspension (25mg) by Boehringer Mannheim revealed that colonic absorption of Carvedilol is about 7 % of that following oral administration. The relative absorption of Carvedilol in jejunum and ileum were 56 % and 28 %, respectively, compared to oral administration. It is believed that the absorption of Carvedilol in the lower GI tract is limited by its pH dependent solubility rather than the permeability.

Formulations

Carvedilol was dosed at 5 mg/kg.

The following three formulations were prepared for the study:

(1) Intracolonic: A solution of Carvedilol-Captisol® complex in water, containing 6% Captisol; Carvedilol concentration, 4.16 mg/mL.

(2) Intracolonic: A suspension of Carvedilol and Encapsin in water, containing 6% Encapsin; Carvedilol concentration, 4.16mg/mL;. (Carvedilol solubility in Encapsin, hydroxypropyl beta-cyclodextrin, is 10 times less compared to Captisol).

(3) Oral suspension: A suspension of Carvedilol in 1% methocel at a concentration of 4.16mg/mL.

InVivo Method

Five male beagle dogs surgically prepared with duodenal and colonic vascular access ports were used. Dogs were dosed at 5 mg/kg at a dose volume of 1.2mL/kg. Vascular access ports were x-rayed for placement and patency prior to and post experiment. Dogs were fasted at least 18 hours prior to dosing. On the day of study, the dogs were placed in a sling (Alice King, Chatham Medical Arts, CA) for the first two hours, and fitted with an indwelling catheters in the forelegs to facilitate blood sampling. After two hours post dosing, the dogs were put back in their cages with free access to water and blood samples taken as appropriate. Food was returned to each dog 8 hours post dosing.

For oral dosing, a 9 mm stomach tubing (20-25 cm) was employed and the dosing solution was followed with 100ml of MilliQ water.

Sample Collection

Three mL blood samples were collected into Vacutainer® labelled heparinized tubes at the following intervals: 0, 7, 15, 30, 45, 60, 90, 120, 240, 360, 480, and 1440 min. All blood samples were placed on crushed ice until ready for centrifugation. Once the plasma was removed, it was placed in cryo tubes and quick frozen on dry ice/methanol and stored at -80°C until subsequent analysis.

Sample Analysis

Dog plasma samples were assayed by levels of carvedilol. Quantitation was performed by LC/MS/MS employing positive-ion electrospray ionisation. A 200microliter aliquot of the

sample was used. The LLQ (lower limit of quantification) was 0.5ng/mL and HLQ (high limit of quantification) was 150ng/mL.

Results and Discussion

The mean plasma concentrations versus time profiles of Carvedilol following bolus oral and intracolonic administration of the various formulations are presented in Figure 1 and Table 1. Figures 2-4 show the plasma concentration of individual dogs following treatment.

As seen from the Table 1, there is no significant difference in the AUC's between the Captisol and Encapsin complexes of Carvedilol administered intracolonically. This is inspite of the fact that Captisol complex is given as a clear liquid, due to its higher aqueous solubility, compared to Encapsin complex being a suspension. It might be speculated that there is not enough fluid in the dog colon to bring about the complete dissociation of the Carvedilol-Captisol complex. The scenario might be different in the human lower GI tract.

Another interesting comparison is the ratio of AUCs of oral versus intracolonic absorption. A 1995 dog study (DDR #47) concluded that intracolonic absorption of carvedilol is about 19% of oral, when a Carvedilol suspension in methocel was dosed at 3mg/Kg.

According to the data presented in Table 2, Captisol and Encapsin complexes show a much higher 60% and 40% respectively, intracolonic absorption compared to oral dosing of a suspension of carvedilol in methocel.

Conclusions

- Carvedilol absorption in the colon is enhanced by its complexation with cyclodextrin.
- Carvedilol absorption in the colon is not significantly different for Captisol and Encapsin complexes.

Table 1
Mean Pharmacokinetic Parameters for Carvedilol Following Oral (PO) and Intracolonic(IC) Administration of Various Formulations in Dogs at 5mg/Kg

Formulation	AUC (ng/mL.min) ± SEM	Cmax (ng/mL) ± SEM	Tmax
PO-Unmilled suspension	281754± 64887	537 ± 65	60
IC-Captisol Solution	110436± 13879	279 ± 31	60
IC-Encapsin Suspension	85159± 14322	163 ± 23	90
Data from DDR#218			
IC-Oleic acid Solution	12800± 7880	32 ± 30	360
IC-Unmilled Suspension	42773± 7368	129 ± 36	90
IC-Milled Suspension	62571± 28810	115 ± 38	90

Table 2
Comparison of Mean AUC's for Carvedilol Following Intracolonic (IC) and Oral (PO) Administration in Dogs at 5mg/Kg.

Formulation	Dog # 2763036	Dog # 3339041	Dog # 2959127	Dog # 3341941	Dog # 2960397	Mean ± SEM
PO- Carvedilol Suspension	212064	174501	852956	66173	103078	281754 ± 64887
IC-Captisol Solution	100000	210748	145472	42334	53629	110436 ± 13879
IC-Encapsin Suspension	41375	112130	199478	41129	31683	85159 ± 14322
Captisol-IC/Oral %	47	121	17	64	52	60 ± 17
Encapsin-IC/ Oral %	20	64	23	62	31	40 ± 10

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A composition comprising a carvedilol-cyclodextrin complex.

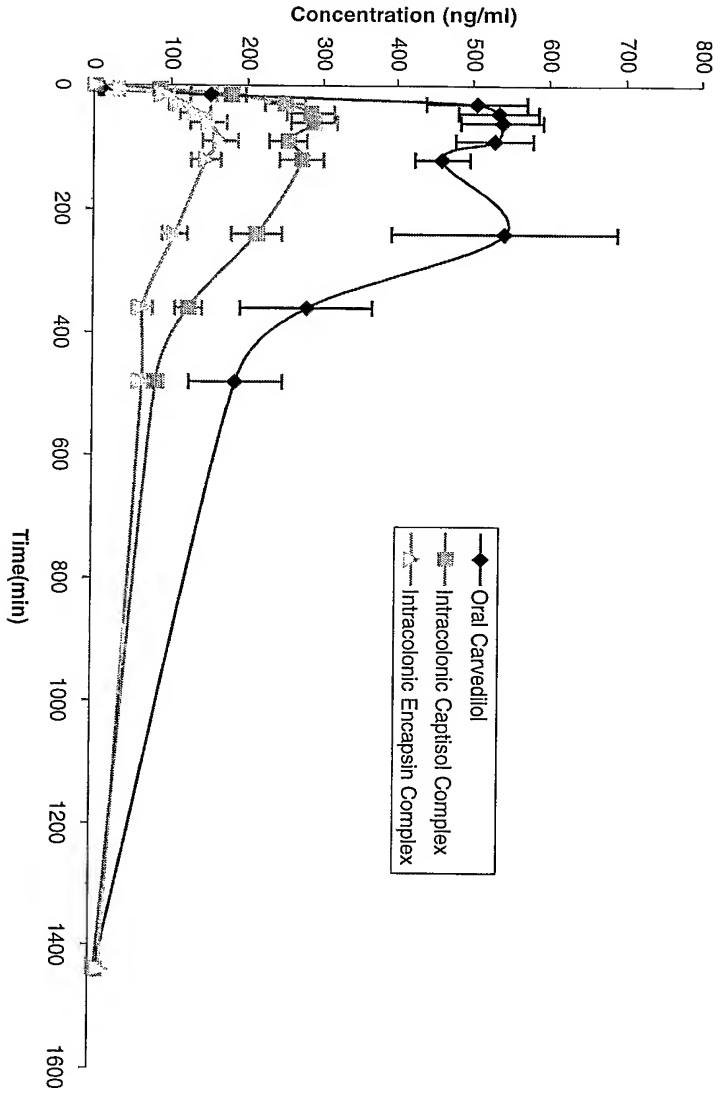
2. The composition according to claim 1 wherein the carvedilol-cyclodextrin complex is Carvedilol-Captisol®.

3. The composition according to claim 1 wherein the carvedilol-cyclodextrin complex is Carvedilol-Encapsin.

4. A formulation in tablet form for oral administration comprising any one of the compositions of claims 1-3.

5. A method of treating hypertension, congestive heart failure or angina which comprises administering to a subject in need thereof an effective amount of the formulation according to claim 4.

6. The use of the composition according to claim 4 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or angina.


Concentration (ng/ml)
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100
200
300
400
500
600
700
800
Time(min)
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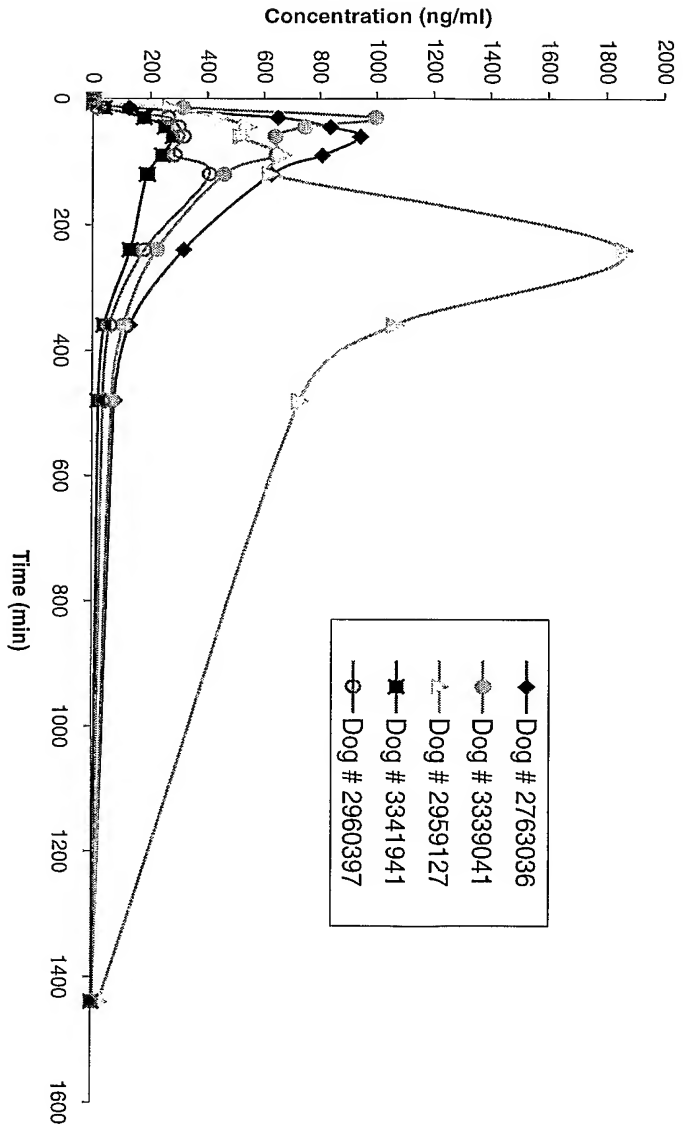
200
400
600
800
1000
1200
1400
1600
Oral Carvedilol
Intracolonic Captisol Complex
Intracolonic Encapsin Complex


Concentration (ng/ml)
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Time (min)
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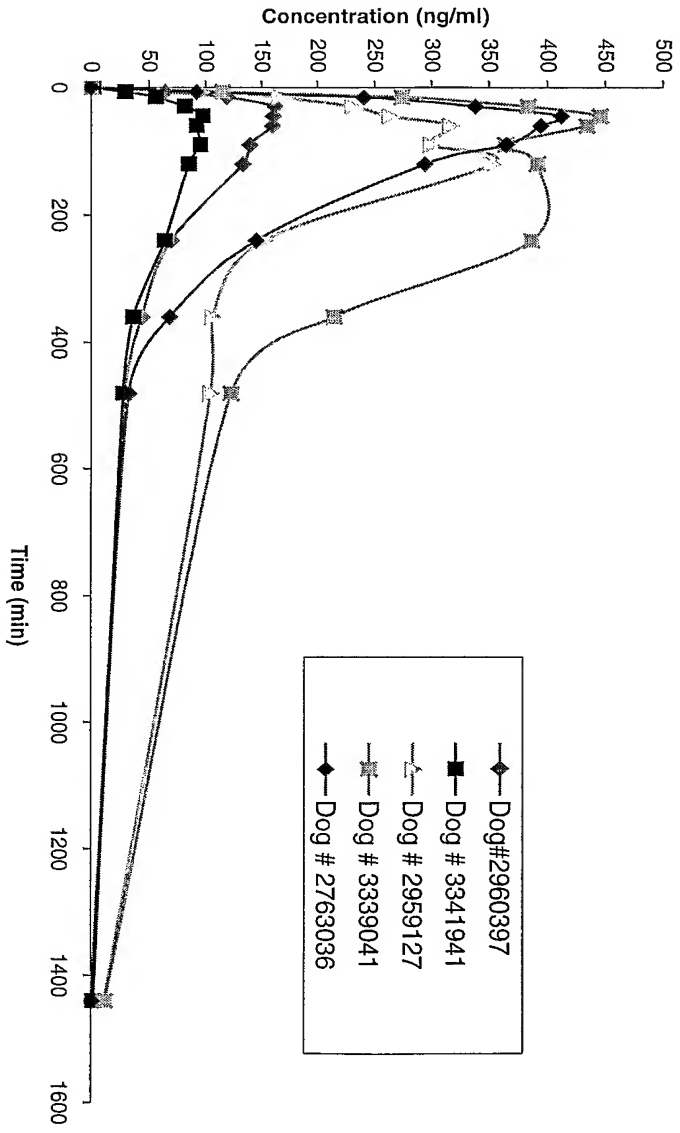
Dog # 3339041
Dog # 2959127
Dog # 3341941
Dog # 2960397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Time (min)
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1600
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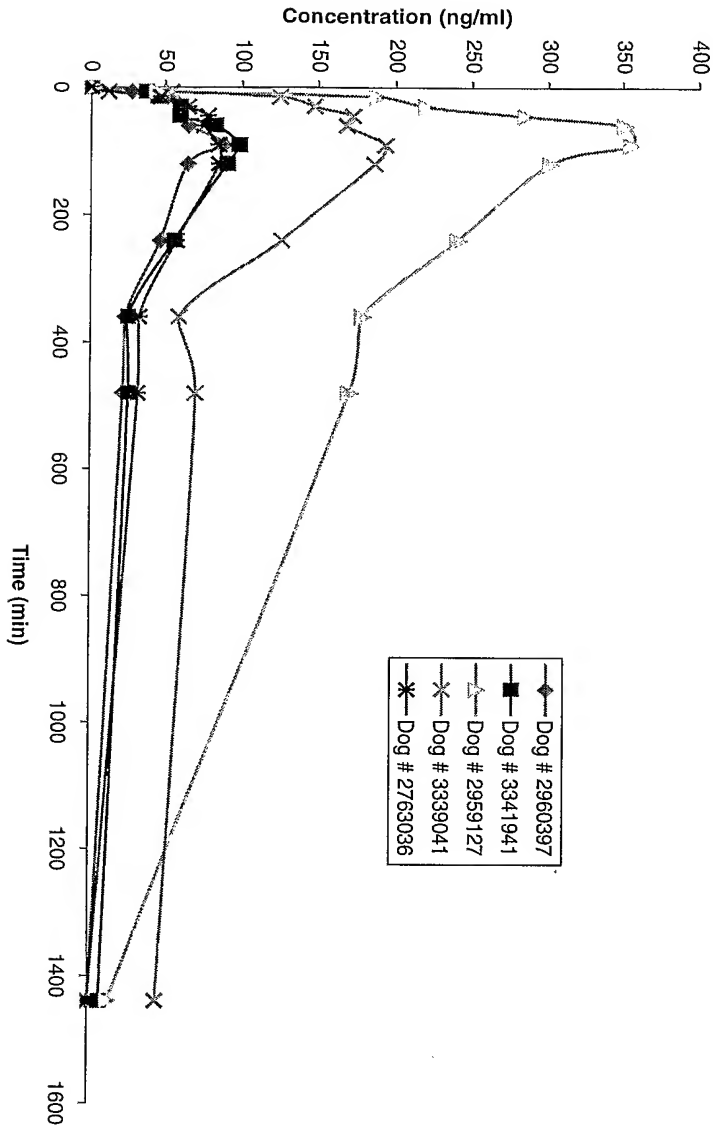
Dog # 2763036


Concentration (ng/ml)
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Time (min)
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600
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1000
1200
1400
1600
Dog # 2960397
Dog # 3341941
Dog # 2959127
Dog # 3339041
Dog # 2763036

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/31297

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/40, 31/735; C07D 401/12
US CL : 514/58, 411
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/58, 411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Merck Index

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,904,929 A (UEKAMA et al) 18 May 1999 (18.05.1999), col. 5, lines 54-55.	1,4-6
Y	US 4,503,067 A (WIEDEMANN et al) 05 March 1985 (05.03.1985), see entire document.	1-6
Y	US 5,902,821 A (LUKAS-LASKEY et al) 11 May 1999 (11.05.1999), see entire document.	1-6
Y	US 5,874,418 A (STELLA et al) 23 February 1999 (23.02.1999), see entire document, specifically col.13, line 64-65.	1-6
Y	US 4,727,064 A (PITHA et al) 23 February 1988 (23.02.1988), see entire document.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
29 November 2002 (29.11.2002)

Date of mailing of the international search report
11 DEC 2002

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